Safety Update on HUMIRA™

Adalimumab for Rheumatoid Arthritis

Arthritis Advisory Committee

March 4, 2003

Presentation Outline

- Introduction
  - James Lefkowith, MD
    Divisional VP, Immunosciences, Abbott
- Overview of clinical efficacy and safety data
  - Steven Fischkoff, MD
    Global Project Head, Arthritis, Abbott
- Review of epidemiological methodology
  - Robert Tarone, PhD
    International Epidemiology Institute, Rockville, MD
- Recommendations
  - James Lefkowith, MD

Consultants

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Professor of Medicine

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Adalimumab

- Adalimumab is a IgG1κ human monoclonal antibody
- Derived using phage display technology
- Neutralizes human TNF-α with high affinity and specificity
- Half-life of approximately 2 weeks similar to endogenous IgG

Approved Indication

- Population
  - Adult patients with moderately-severely active RA
  - Inadequate response to prior DMARDs
- Indication
  - Reduction in signs and symptoms
  - Inhibition of the progression of structural damage
- Usage
  - Monotherapy or combination with DMARDs
  - 40 mg sc every other week

Warnings in Package Insert

- Boxed warning
  - Tuberculosis
- Warnings
  - Serious infections (tuberculosis)
  - Demyelinating disorders
  - Malignancies and lymphoma

Serious Adverse Events

- Differences in case capture rates and quality of data:
  - Controlled trials
  - Registries
  - Post-marketing reports
- Patient variation
  - Baseline demographics (age, sex, race, geography)
  - Disease severity or duration

Overview of Clinical Program, Efficacy and Safety Data

Steven Fischkoff, MD
Global Project Head, Arthritis
Abbott Laboratories

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- Clinical program
  - Baseline demographics and disease severity
- Efficacy
  - Signs and symptoms
  - Radiographic progression
  - HAQ-related disability
- Safety
  - Tuberculosis
  - CNS demyelination
  - Congestive heart failure
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- Post-marketing commitments

Clinical Safety Database

- Program size (31-Aug-2002)
  - 2468 RA patients on adalimumab
  - 4870 pt-year exposure
- Studies
  - 20 studies in RA, 4 pivotal
  - 1380 adalimumab patients in pivotal studies
- Length of follow-up
  - 1990 patients followed >1 yr
  - Median exposure 2 years
  - >40 patients in 6th year of therapy

Pivotal Studies

	With Methotrexate		Monotherapy	With DMARDs
	DE009 (N=271)	DE019 (N=619)	DE011 (N=544)	DE031 (N=636)
Doses (mg)	Placebo	Placebo	Placebo	Placebo
eow	20/40/80	40	20/40	40
weekly		20	20/40	
Primary Endpoint				
Signs/Symptoms	6 months	6 months	6 months	
HAQ		12 months		
X-rays		12 months		
Safety 1% AE rate				6 months

eow = every other week

Baseline Demographics and Disease Severity – Pivotal Trials

	TOTAL (N=2070)	DE009 (N=271)	DE019 (N=619)	DE011 (N=544)	DE031 (N=636)
Age (yrs)	55	55	57	53	55
Duration of RA (yrs)	11	12	11	11	10
# of prior DMARDs	2.8	3.0	2.4	3.7	2.2
Corticosteroid use (%)	55	49	46	71	53
TJC (0-68)	30	29	28	34	28
HAQ (0-3)	1.6	1.6	1.5	1.9	1.4
CRP (0-0.8 mg/dL)	2.8	2.7	1.7	5.2	1.5

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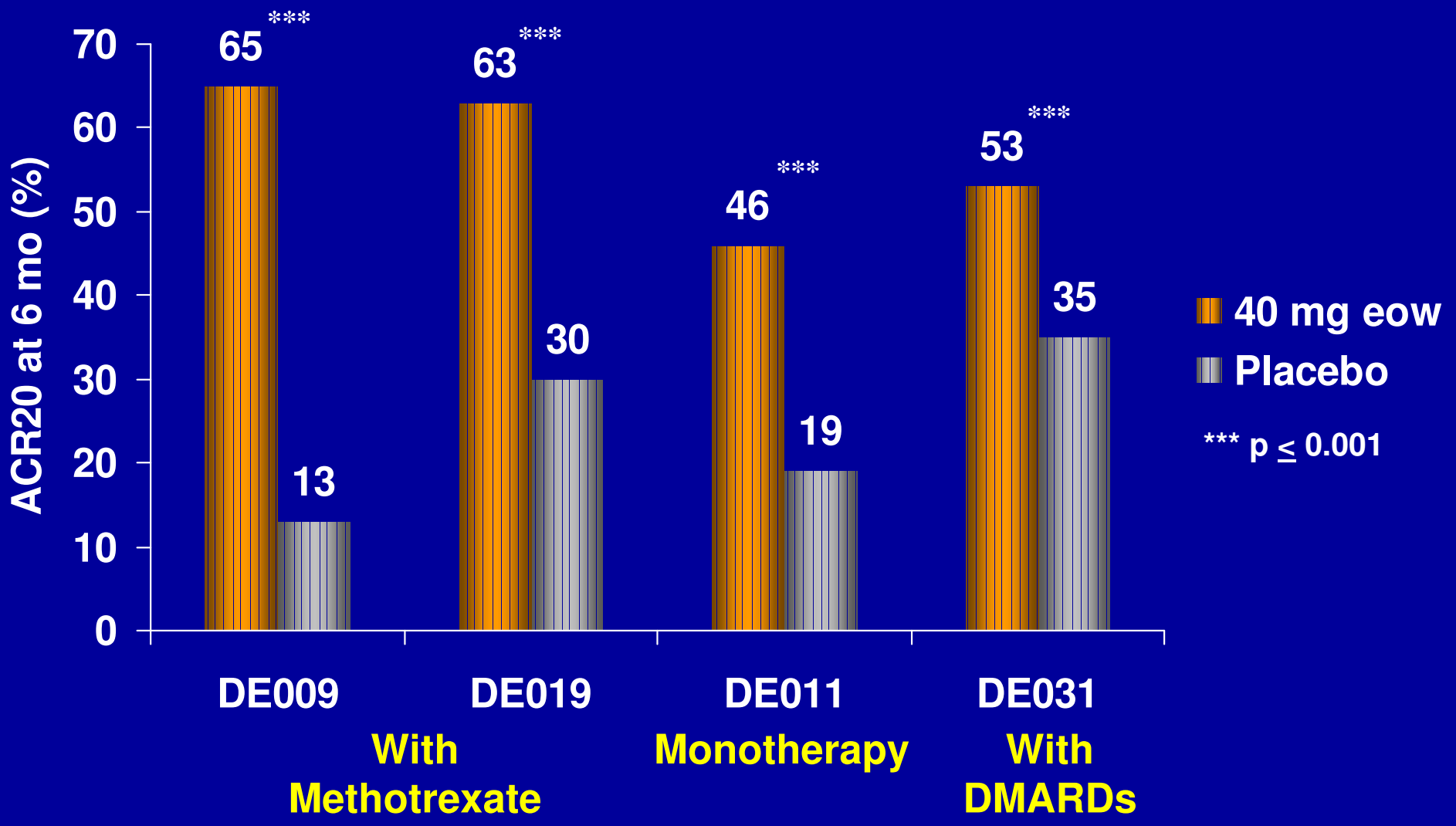
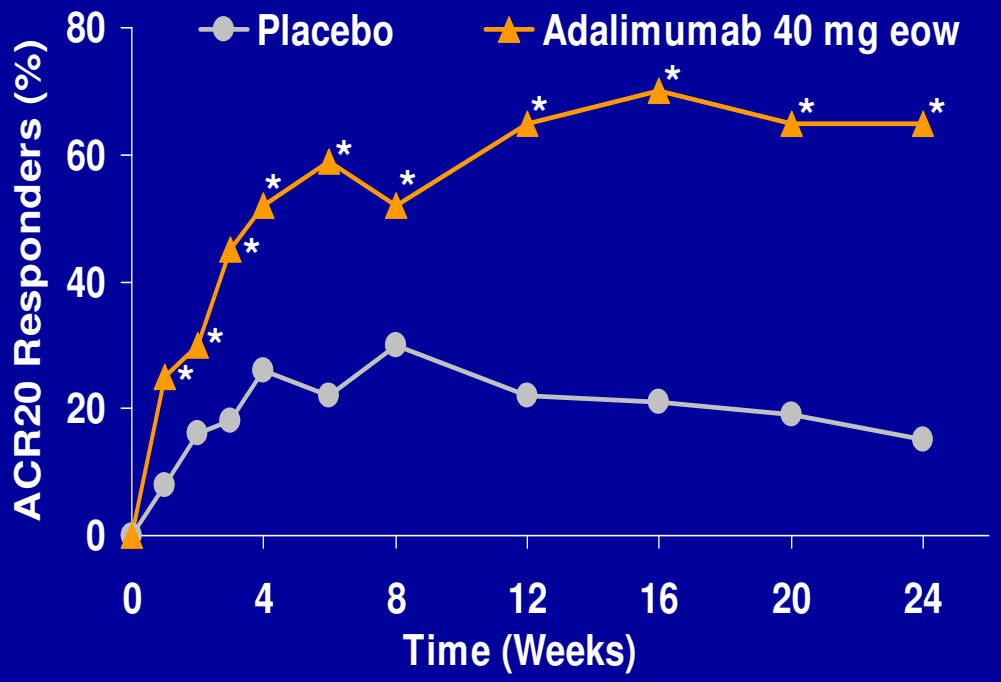
Efficacy: Signs and Symptoms

ACR20 Response at 6 Months



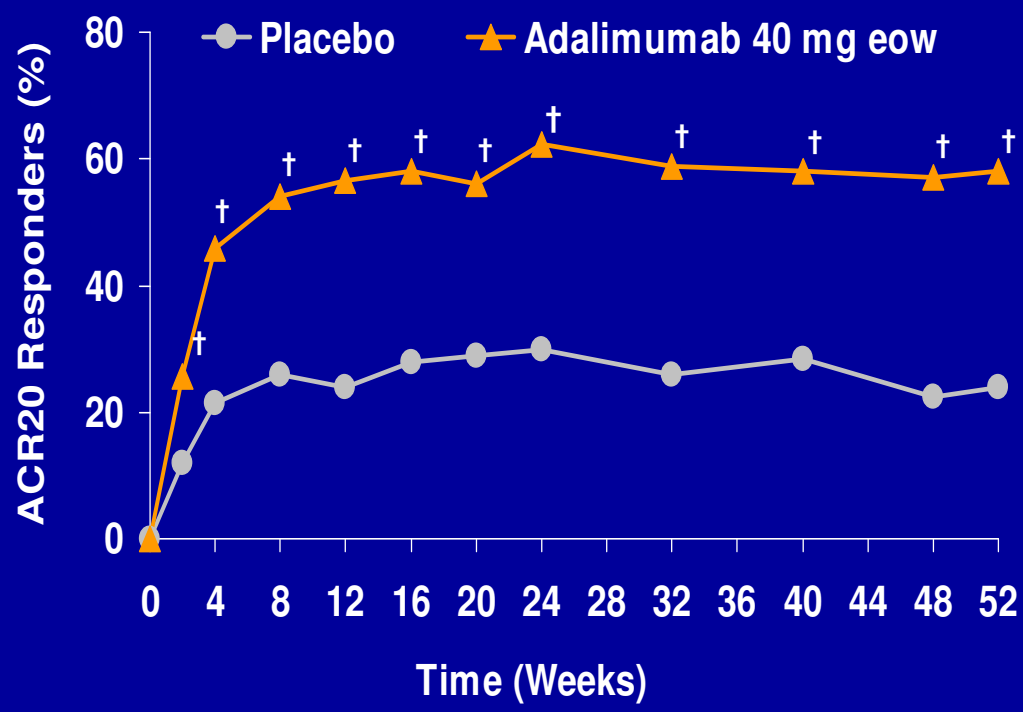
Time Course of ACR20 Response

Study DE009 (24 weeks)



*p≤ 0.05 vs. placebo at all time points

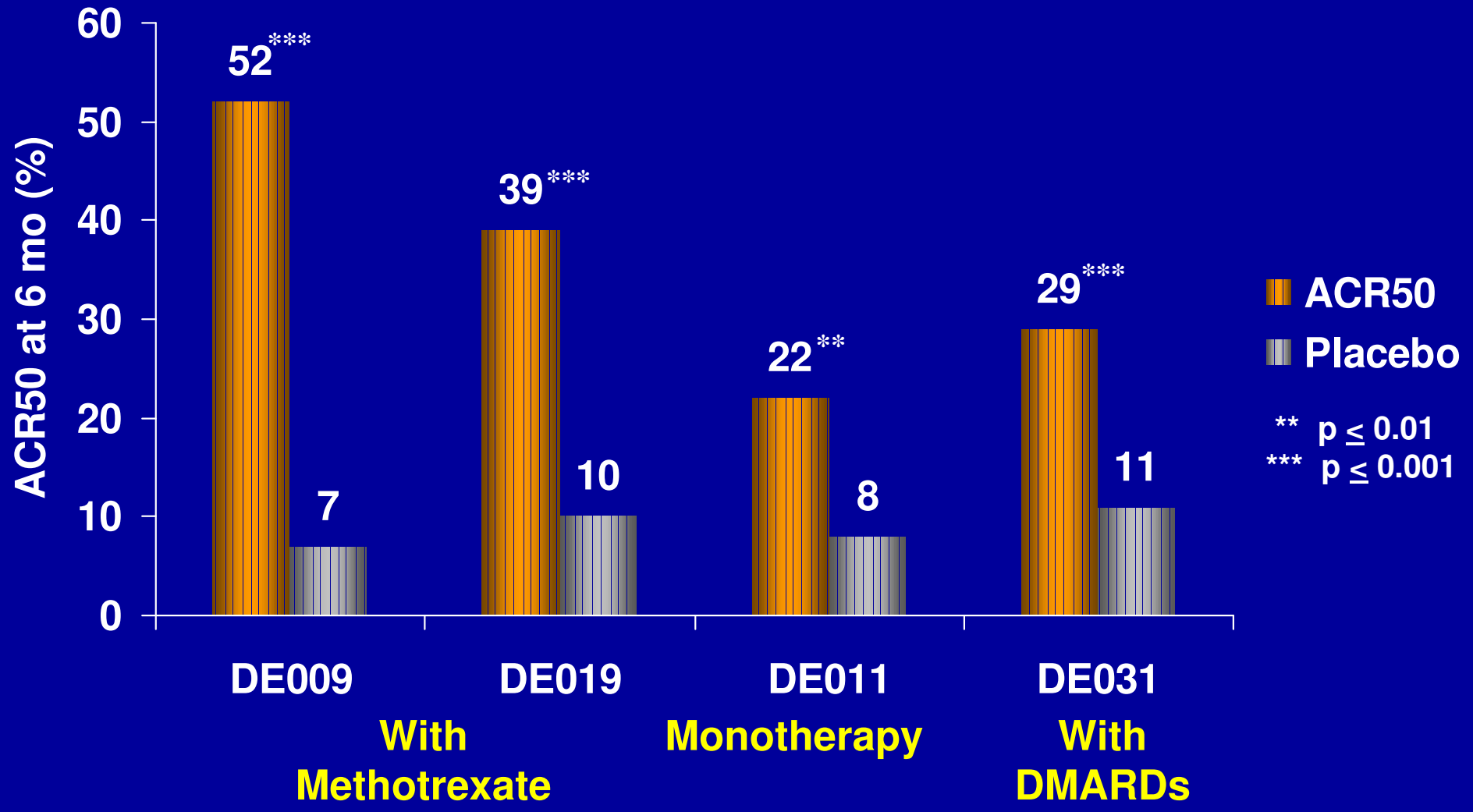
Study DE019 (52 weeks)



†p ≤ 0.001 compared to placebo at all time points

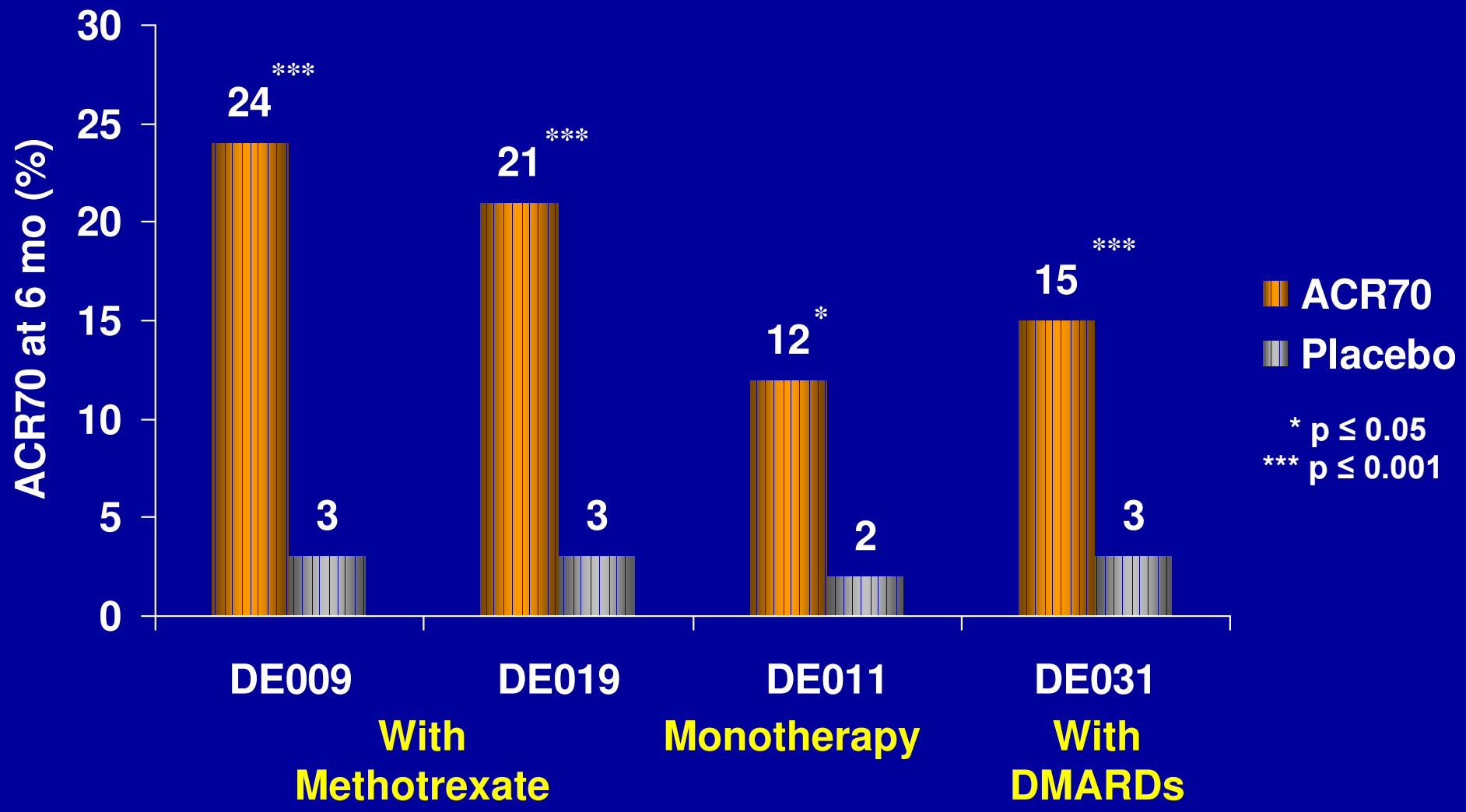
Efficacy: Signs and Symptoms

ACR50 Response at 6 Months



Efficacy: Signs and Symptoms

ACR70 Response at 6 Months



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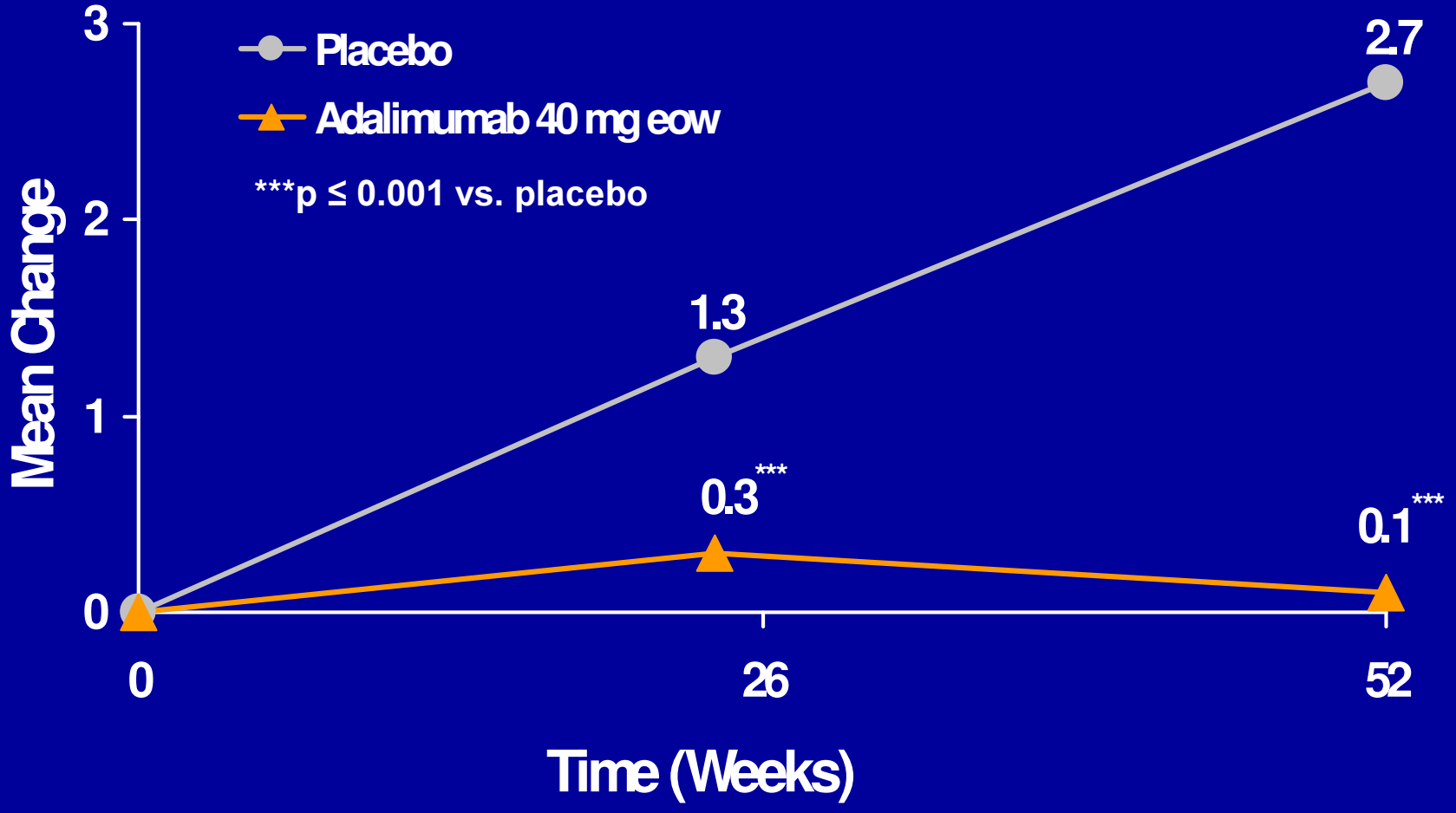
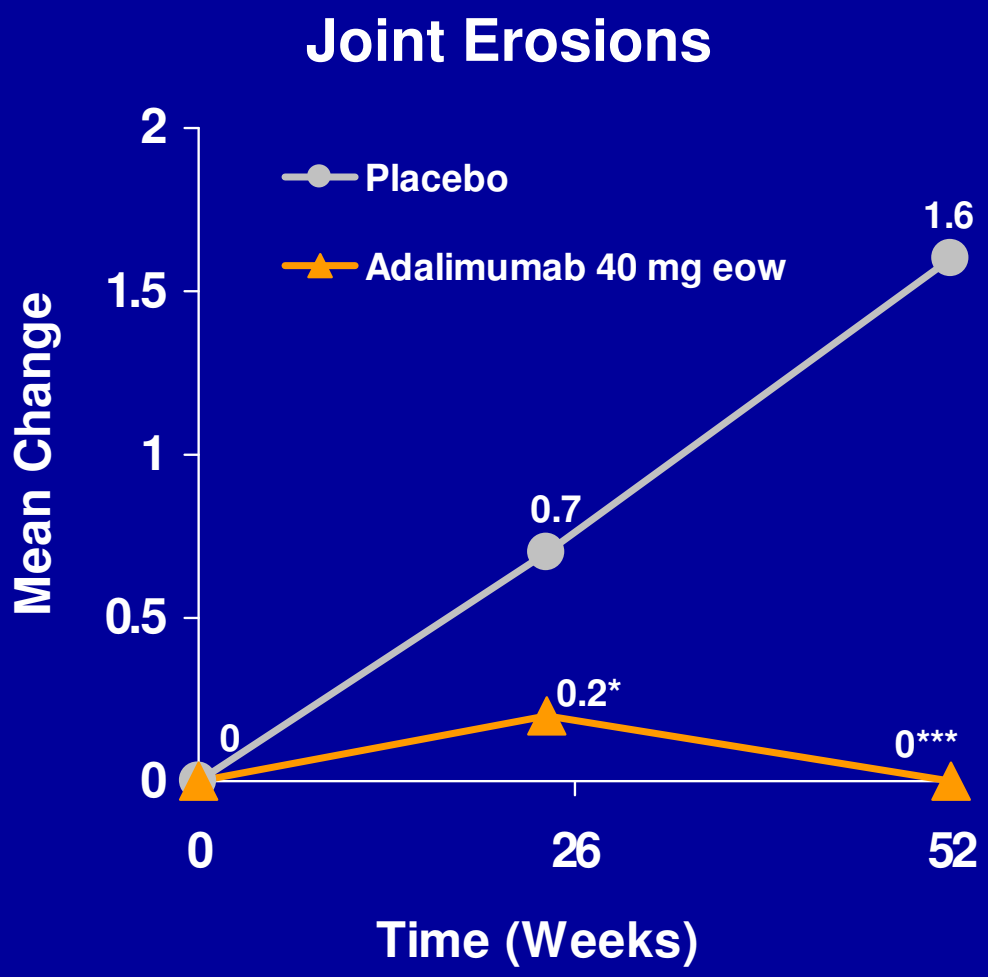
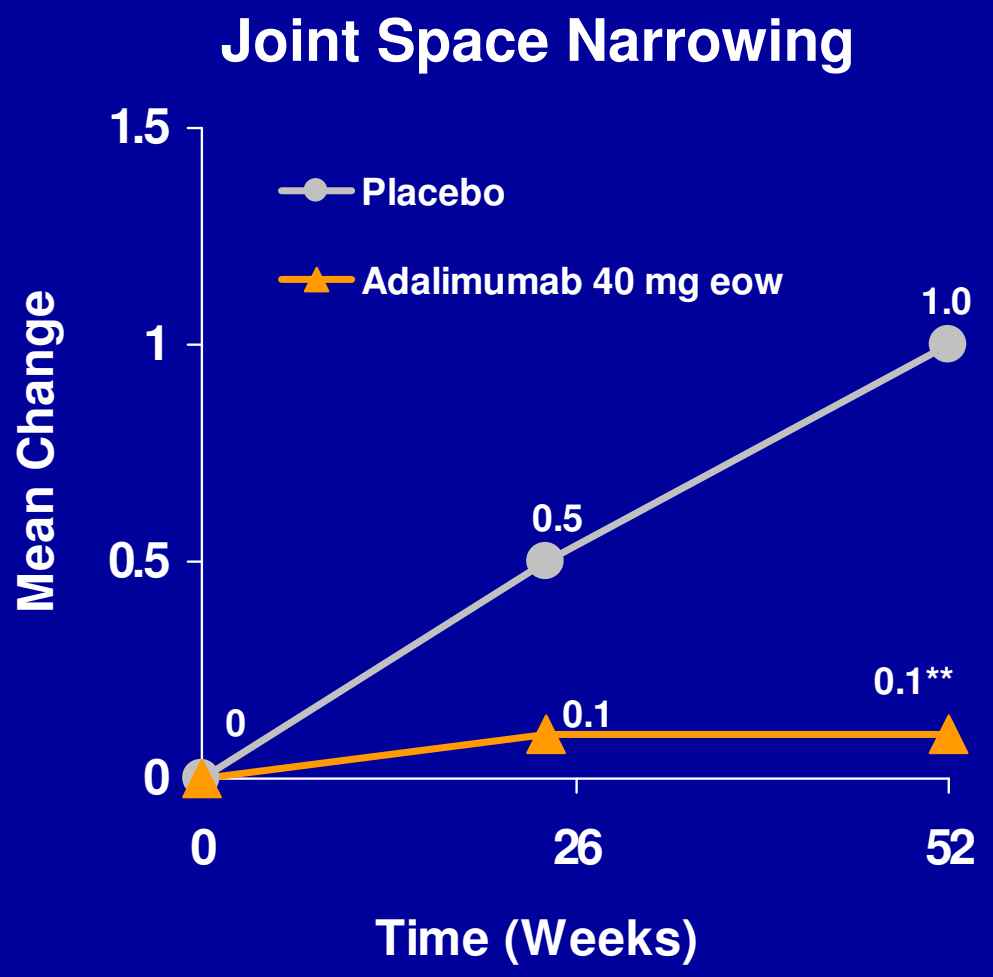
DE019: Inhibition of Progression of Structural Damage

Change in Modified Total Sharp Score



DE019 Radiographic Changes at Weeks 24 and 52





* p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001 vs. placebo

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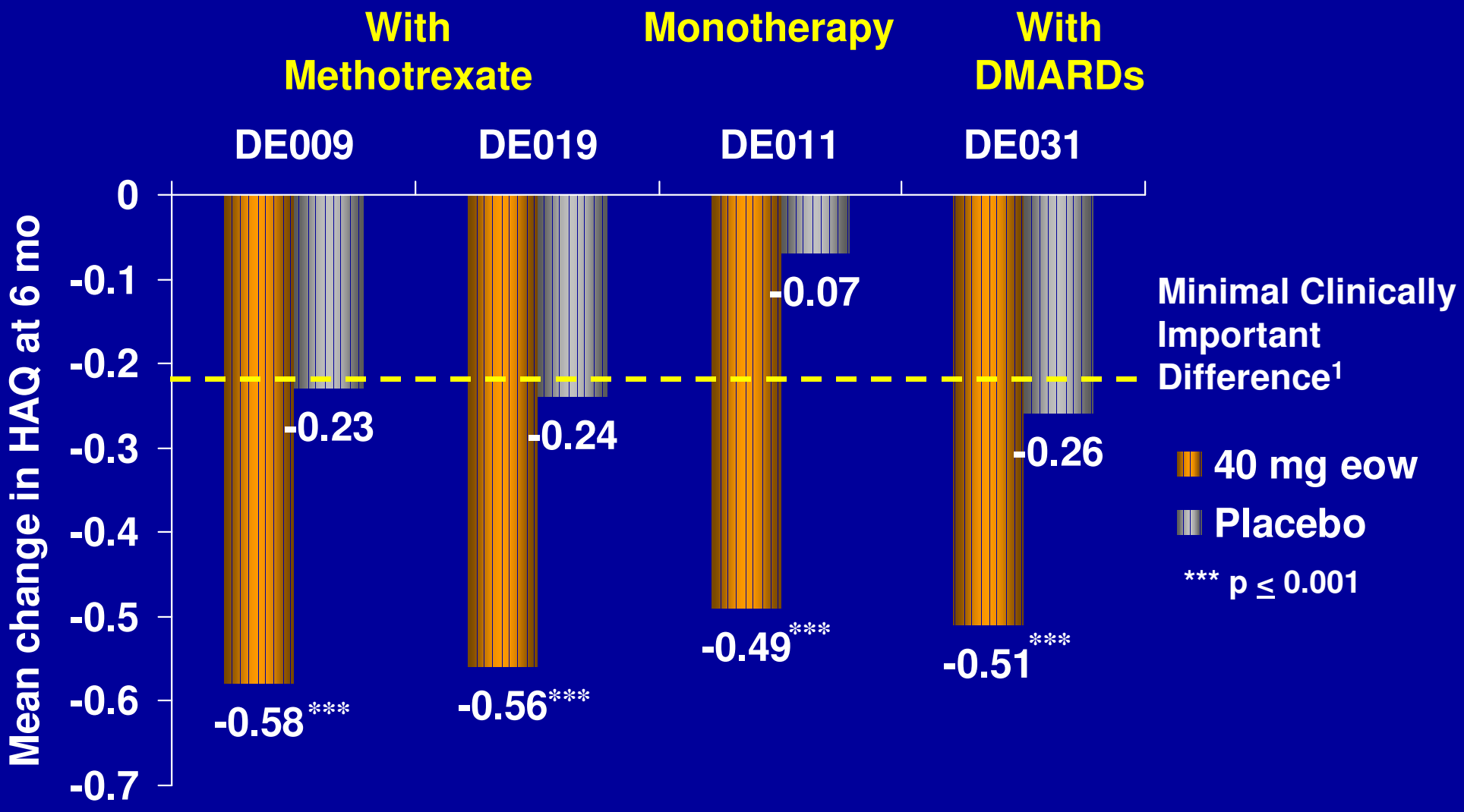
Disability Index of HAQ

Change in HAQ at 6 Months



[1]Goldsmith, et al. *J Rheum* 1993;20:561-565.

Adalimumab – Efficacy Conclusions

- Reduces signs and symptoms of RA
  - ACR20/50/70
- Inhibits progression of structural damage of RA
  - Total Sharp Score
  - Joint Erosion Score
  - Joint Space Narrowing Score
- Provides rapid onset and durable response
- Improves Disability Index as measured by HAQ

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Tuberculosis: Literature

- TB seen with all TNF-antagonists[1-5]
  - Consistent with preclinical data (antibodies, receptor constructs)
  - Unusual clinical presentation
  - Post-marketing reports underestimate true incidence
  - Geography and patient demographics impact rates
- Clinicians should be alert to the possibility of TB[4-6]
  - Screening for latent TB recommended for all TNF-antagonists

[1]Flynn, et al. *Ann Rev Imm* 2001;19:93-121.
[2]Garcia, et al. *Eur J Imm* 1997;27:3182-3190.
[3]Mohan, et al. *Inf Imm* 2001;69:1847-1855.
[4]Manada, et al. *Arthritis Rheum* 2002;46 (Suppl):S166.
[5]Keane, et al. *NEJM.*, 2001;345:1098-1104.
[6]Furst, et al. *Ann Rheum Dis* 2002;61:(Suppl II):ii-ii7.

Tuberculosis: All Trials

- 13 cases of TB in patients on adalimumab
  - Germany (6), EU other (4), US (2), Canada (1)
- 3 cases of TB observed in patients not on adalimumab therapy
  - Germany (2), Italy (1)
- Incidence
  - Peak: 3-8 mos
  - Infrequent cases >1 y
- All patients recovered with standard therapy

Tuberculosis: Impact of Screening Adalimumab-treated Patients

Phases	Screening	TB Cases[1]
I/II (N = 479)	No	8
III (N = 1380)	Yes	1[2]

[1]4 cases seen in Open-Label Extensions/IIIb; 2 had baseline evidence of latent TB infection

[2]Negative PPD and CXR at baseline (primary TB)

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CNS Demyelination: Literature and All Trials

- CNS demyelination has been reported with TNF-antagonist therapy[1]
- 4 cases seen with adalimumab
  - 1 presented with optic neuritis
  - 3 presented with paresthesias
    - 1 patient had prior MS
- All cases resolved (1 partial)
  - 1 corticosteroids, 1 Copaxone®, 2 spontaneously

[1]Mohan, et al. *Arthritis Rheum* 2001;44:2862-2869.

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Incidence of Congestive Heart Failure in Pivotal Studies

	Placebo N (%)	Adalimumab N (%)
Prior history of CHF	7	18
Relapse CHF	0 (0)	0 (0)
No prior history of CHF	683	1362
New onset CHF	5 (0.7)	2 (0.1)

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Malignancies: Literature

- Cancer risk impact of TNF antagonism is unclear
- Evidence suggesting increased cancer risk[1]
  - Immune surveillance for cancer
  - Supraphysiologic doses can induce tumor regression
- Evidence suggesting lowered cancer risk[1]
  - TNF-deficient mice are resistant to skin carcinogenesis
  - TNF is a growth factor for several lymphoma and leukemia cell lines

[1]Balkwill, *Cytokine Growth Factor Res.* 2002;13:135-141.

Malignancy Incidence: All Trials

- Rate of cancer consistent with matched population using 1992-1999 SEER database (which excludes non-melanoma skin cancer)
  - 45.5 expected based on SEER statistics adjusting for age, sex and race
  - 46 cancers observed
  - SIR = 1.0 (95% CI 0.7-1.3)

SEER = Surveillance, Epidemiology, and End Results (network)
SIR = Standardized Incidence Ratio

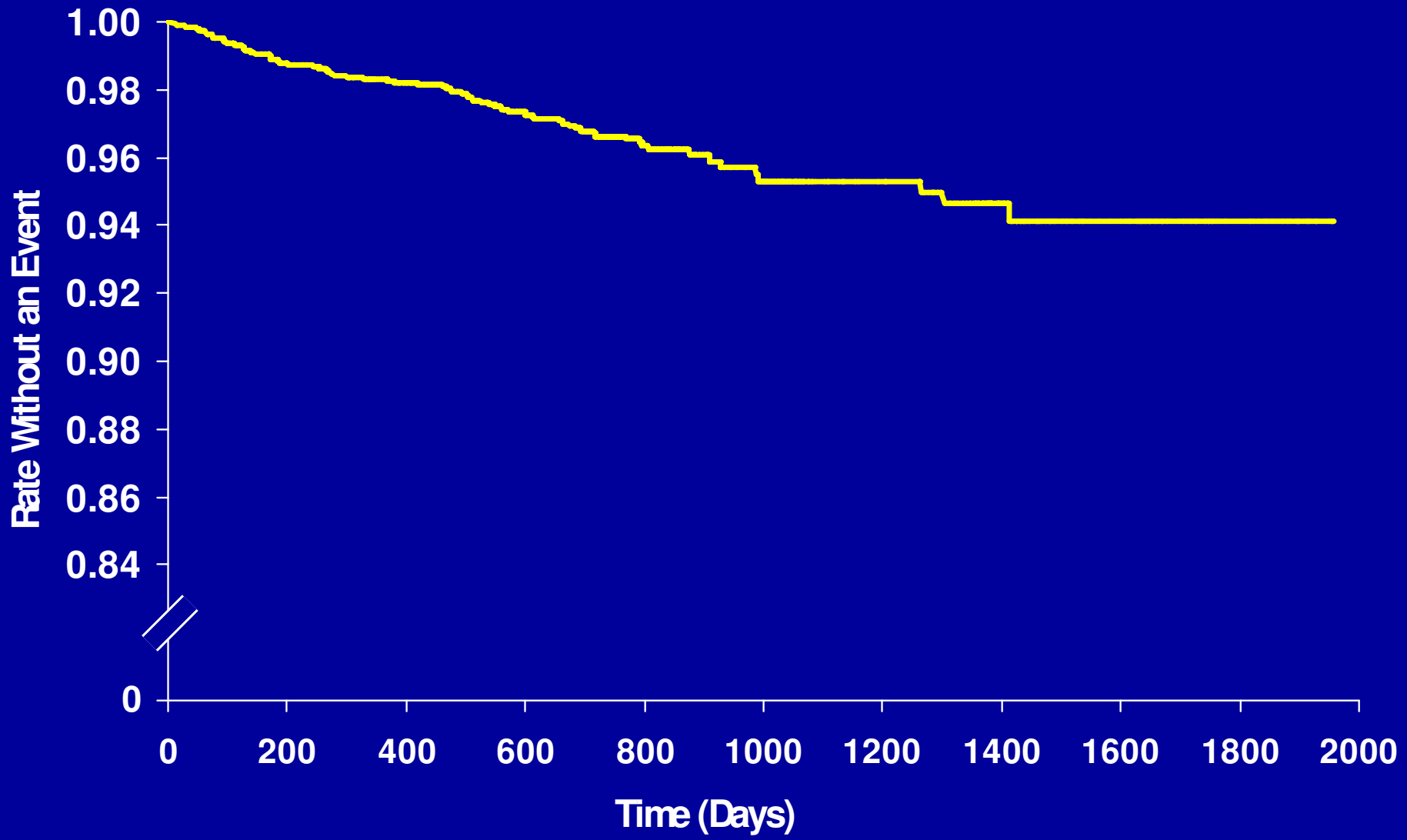
Malignancy Types: All Trials

Solid tumors except non-melanoma skin cancer

Cancer type	Observed	Expected[1]	SIR	95% CI
All Sites	46	45.5	1.0	0.7 - 1.3
All Lymphomas	10	1.8	5.5	2.6 - 10.0
Breast	7	11.0	0.6	0.3 - 1.3
Colon	5	4.8	1.1	0.3 - 2.4
Prostate	5	4.5	1.1	0.4 - 2.6
Uterine	4	2.3	1.8	0.5 - 4.6
Melanoma	3	1.5	2.1	0.4 - 6.0
Lung	1	6.6	0.2	0.0 - 0.8
Other Sites	11	13.1	0.8	0.4 - 1.5

[1]Cancer rates used were 1992-1999 SEER Rates

Time to First Malignancy
All RA Patients Treated with Adalimumab (N=2468)



Lymphoma Incidence in RA: Literature

Study	Country	Number of RA Patients	Years of follow-up	SIR for Cancer	SIR for Lymphomas (OR/Activity Level)
Gridley 1993	Sweden	11,683	20	1.0	2.0
Mellenkjaer 1996	Denmark	20,699	14	1.1	2.5
Isomaki 1978	Finland	46,101	7	1.1	2.7
Baecklund 1998	Sweden	11,683	18	–	(1.0/Low) (5.4/Med.) (25.8/High)
Wolfe 1994	US and Canada	3501	35	0.3	8.0
Matteson 1991	Canada	530	7	1.5	8.0

OR = odds ratio

Disease Activity Scoring Baecklund et al.

Score at each visit	1	2	3
ESR	1-30	31-60	61-150
Number of swollen and tender joints	0-3	4-6	7+
Physician's global assessment of disease activity	Mild	Moderate	Severe
Mean score from all visits	0-4	>4-8	>8
Final evaluation of disease activity	Low	Medium	High

Baecklund, et al. *BMJ* 1998;317:180-181.

Lymphoma Incidence in RA: Literature and All Trials

Study	Country	Number of RA Patients	Years of follow-up	SIR for Cancer	SIR for Lymphomas (OR/Activity Level)
Gridley 1993	Sweden	11,683	20	1.0	2.0
Mellenkjaer 1996	Denmark	20,699	14	1.1	2.5
Isomaki 1978	Finland	46,101	7	1.1	2.7
Adalimumab 2002	Global	2468	5	1.0	5.5 (Med./High)
Baecklund 1998	Sweden	11,683	18	–	(1.0/Low) (5.4/Med.) (25.8/High)
Wolfe 1994	US and Canada	3501	35	0.3	8.0
Matteson 1991	Canada	530	7	1.5	8.0

OR = odds ratio

Cell Type of Lymphoma in RA Patients

	Adalimumab N=10	Kamel N=42	Baecklund N=35
B Cell	80%	98%	91%
T Cell	10%	2%	3%
Hodgkin's	10%	N/A	6%

Kamel, et al. *J Rheum* 1999;26:1676-1680.

Baecklund, et al. *Ann Rheum Dis* 2001;60:(Suppl 1)73.

Histology of NHL in RA Patients

	Adalimumab N=9	Kamel N=42	Baecklund N=33
Diffuse B Cell	56%	52%	67%
Follicular B Cell	11%	33%	6%
Peripheral T Cell	11%	2%	3%
Other	22%	13%	24%

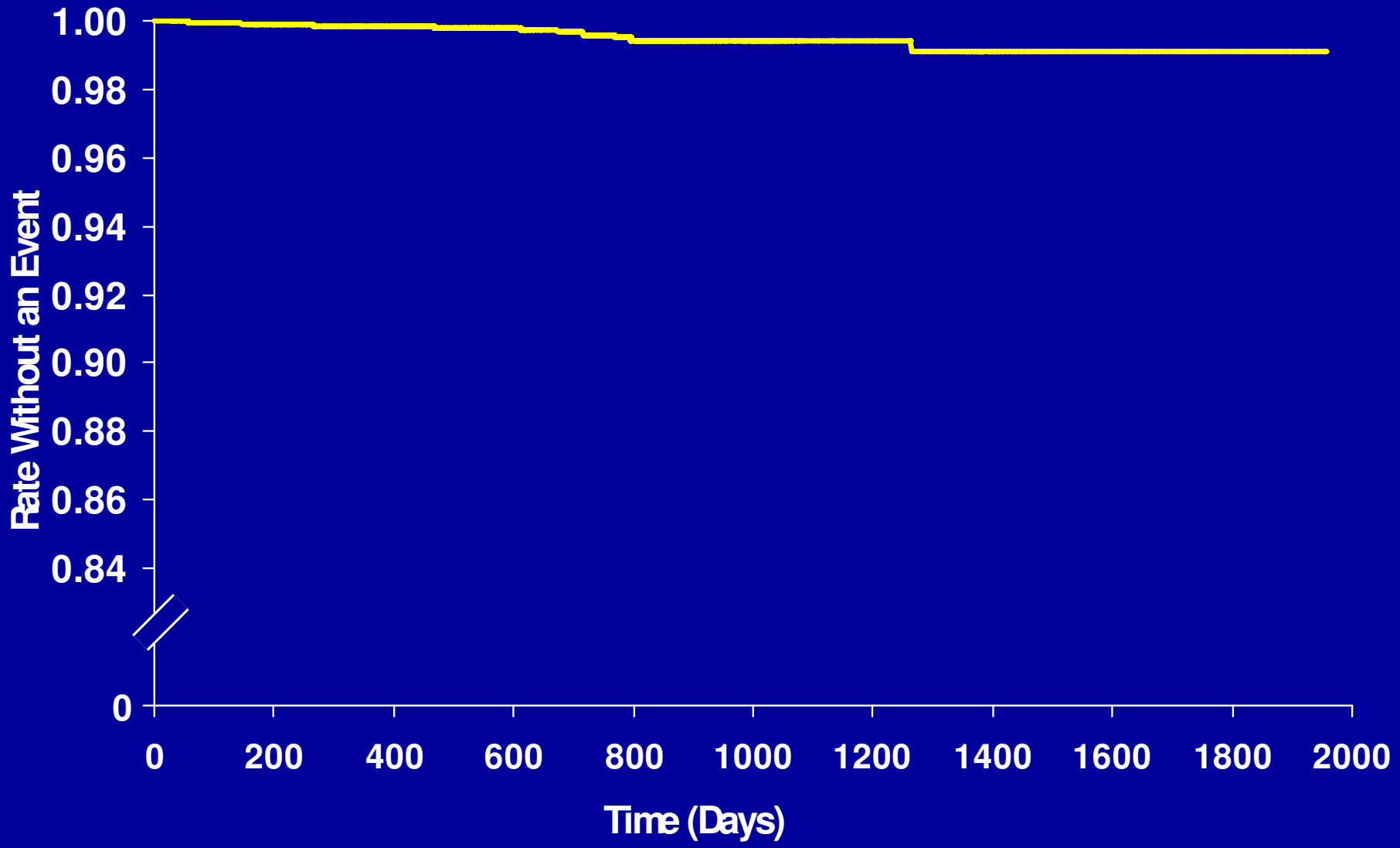
Kamel, et al. *J Rheum* 1999;26:1676-1680.

Baecklund, et al. *Ann Rheum Dis* 2001;60:(Suppl 1)73.

Lymphoma Histology: All Trials

Cell Type	Age	Yrs RA	# Prior DMARD	Bsln TJC
B cell - Mixed small and large	62	7.3	2	50
B cell - Mixed small and large	68	20.8	4	17
B cell - Large Cell Diffuse	56	4.3	3	6
B cell - Large Cell Diffuse	59	17.0	1	25
B cell - Diffuse Large Cell	75	2.8	1	16
B cell - Follicular with sclerosis	71	29.9	2	34
B cell - MALT, poss. Sjogren's	39	6.6	4	42
B cell - Mantle Cell	58	13.2	5	46
T cell - Low-intermediate grade	64	2.9	1	24
Mixed cellularity Hodgkin's	75	19.9	3	54
Mean	63	12.5	3	31

Time to First Lymphoma
All RA Patients Treated with Adalimumab (N=2468)



Safety Conclusions

- All TNF-antagonists, including adalimumab, are associated with a risk of TB
  - Screening is effective in reducing the incidence of TB and is standard of care
- Rare cases of CNS demyelination observed
- Malignancy rate similar to matched general population
- Lymphoma rate similar to matched RA population

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Post-Marketing Commitments: RA

- Commitment to continue long-term safety trials in ~1700 patients for 5 years
  - Safety data collection monitored
  - Increase clinical trial database by 2-fold
  - Precise calculation of incidence rates
- European registry with approximately 3000-5000 patients from expanded access programs
  - Provides large experience to detect rare events

Post-Marketing Commitments, New Indications and Spontaneous Reporting

- Additional clinical trials
  - JRA, early RA
  - Crohn's disease
  - Psoriasis and Psoriatic arthritis
  - Ankylosing spondylitis
- Spontaneous post-marketing reporting
  - Variable and less complete case capture precludes precise calculation of incidence rates for comparisons
  - Detection of rare new signals or change in patterns

Overall Assessment: Benefits and Risks

- Adalimumab is effective in
  - Reducing the signs and symptoms of RA
  - Inhibiting the progression of joint destruction
- TNF-antagonists have been associated with rare cases of TB and CNS demyelination
  - Guidance in adalimumab physician/patient insert
- Adalimumab does not contribute to increased risk of cancer or lymphoma in the RA population
- Benefit risk assessment for adalimumab is highly positive and represents a significant contribution to the care of RA patients

Epidemiologic Methodology

Robert Tarone, Ph.D.
International Epidemiology Institute
Bethesda, MD

SEER: Surveillance, Epidemiology & End Results

- NCI program is the authoritative source of information on cancer incidence and survival in the US.
- Population-based cancer registries – attempts to ascertain all primary cancers diagnosed within boundaries of SEER catchment areas (defined by county or state lines).
- 11 registries since 1992, covering approximately 14% of the US population.
  - In 2003, there will be data from 4 additional registries with total coverage of 26% of the US population (24% African-Americans, 44% of Hispanics, 59% Asian-Americans).
- Sex-specific, race-specific cancer incidence rates in 5-year age intervals through ages 80-84.

Standardized Incidence Ratio (SIR)

- We use the SEER incidence rates for 1992-1999; race-specific, sex-specific, and age-specific in 5-year age intervals.
- y = each year (or fraction thereof) a person is followed at a given age for diagnoses of cancer.
- r = annual incidence rate of cancer at that age in the general population.
- $y \times r$ = contribution to the expected number of cancers.

Standardized Incidence Ratio (SIR)

- Consider a white man with first adalimumab injection at age 79 years and 3 months who is followed for 2.5 years.

- The lymphoma rate for 75-79 years of age is 119.8 per 100,000 and the man is followed for 0.75 year in the 75-79 age interval: his first contribution to the expected value is:

$$y \times r = 0.75 \times 119.8 = 89.9 \text{ per } 100{,}000.$$

Standardized Incidence Ratio (SIR)

- The lymphoma rate for 80-84 years of age is 131.1 per 100,000 and the man is followed for 1.75 years in the 80-84 age interval: his second contribution to the expected value is:

  $y \times r = 1.75 \times 131.1 = 229.4$ per 100,000.

- His total contribution to the expected number of lymphomas is:

  $E_j = 89.9 + 229.4 = 319.3$ per 100,000 or 0.0032.

Standardized Incidence Ratio (SIR)

- Let the contribution for the j^{th} patient in the adalimumab trials be denoted by E_j ; the expected number of lymphomas in all patients in the trials is the sum of the E_j for all 2468 patients.

$$\sum_{j=1}^{2468} E_j$$

- The SIR is the ratio of the observed number of lymphomas to the number of lymphomas expected in all patients.

Adalimumab Trials
Standardized Incidence Ratios

	Observed	Expected	SIR (95% CI)
All cancer	46	45.5	1.0 (0.7-1.3)
Lymphoma	10	1.8	5.5 (2.6-10.1)
NHL	9	1.7	5.4 (2.5-10.2)
Hodgkin's Disease	1	0.1	7.2 (0.1-40)
Other cancer	36	43.7	0.8 (0.6-1.1)

Labeling Considerations

James Lefkowith, MD
Divisional VP, Immunosciences
Abbott Laboratories

Evaluating Risk: Differences between Post-Marketing and Controlled Trials

Type of Trial	Patient Population	GI Event Rate (/100 pt yrs)
Post-Marketing	OA/RA	0.02-0.04[1]
Clinical Trial	OA/RA	2-4[2]

Are these differences in event rates real?

[1]Paulus, H.E. A&R 1985;28:1168-1169.
[2]Paulus, H.E. A&R 1988;31:1450-1451.

Labeling Recommendations

- Highlight information on prevention/screening
- Harmonize information on vigilance
- Describe rates with adequate context information
  - Patient characteristics and nature of study design
  - Caveat regarding limitations on comparability between products
- SIRs are useful for describing cancer risks
  - NCI SEER database is an appropriate comparator: 1992-1999 version corrected for age, sex, race
  - Must come from study allowing complete data capture
- Absolute vs relative risk